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Review

# Glycosphingolipids and drug resistance

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**Abstract**

Drug resistance, an all too frequent characteristic of cancer, represents a serious barrier to successful treatment. Although many resistance mechanisms have been described, those that involve membrane-resident proteins belonging to the ABC (ATP binding cassette) transporter superfamily are of particular interest. In addition to cancer, the ABC transporter proteins are active in diseases such as malaria and leishmaniasis. A recent renaissance in lipid metabolism, specifically ceramide and sphingolipids, has fueled research and provided insight into the role of glycosphingolipids in multidrug resistance. This article reviews current knowledge on ceramide, glucosylceramide synthase and cerebrosides, and the relationship of these lipids to cellular response to anticancer agents.


*Keywords:* Multidrug resistance; Glycosphingolipids; Glucosylceramide synthase; P-glycoprotein

**Contents**



## 1. Introduction

The phenomenon of biocide and drug resistance arising in biological systems is widespread. With surprising rapidity, organisms evolve defenses to protect themselves from toxins of all kinds. Increasingly, drug-resistant bacteria and viruses (for example, tuberculosis, *Staphylococcus*, HIV), pesticide-resistant insects (lice, mosquitoes), and herbicide-resistant weeds pose a serious and growing threat to human health and the ecosystem. Although many resistance mechanisms have been described, those that involve membrane proteins belonging to the ABC transporter superfamily are best understood. These proteins play a major role in such devastating and widespread diseases as malaria, leishmaniasis, and cancer, as they can impact drug disposition and modulate drug interactions [1–6].

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## 2. Drug resistance and ABC transporter proteins

Overexpression of the membrane efflux transporter P-glycoprotein (P-gp), an ATP-binding cassette (ABC) transporter protein, is one of the most consistent biological alterations in drug resistance [1,7,8]. ABC proteins contain a hydrophobic membrane-spanning domain with as many as six transmembrane helices and a hydrophobic cytosolic nucleotide-binding domain [9]. P-gp (gene symbol ABCB1), a 170 kDa protein, was the first ABC protein demonstrated to confer resistance to natural product agents used in the treatment of cancer [10,11]. In humans P-gp is encoded by the *MDR1* gene [12]. A second ABC protein, a 190-kDa membrane glycoprotein called MRP1 (multidrug resistance protein, gene symbol ABCC1), was discovered shortly thereafter [13]. A more recently described transporter is breast cancer resistance protein (BCRP, gene symbol ABCG2), which must homodimerize to acquire transport activity [14,15]. Although P-gp and related transporters all reduce the intracellular concentration of antitumor, antiviral, and antibacterial agents via ATP-dependent effluxing, these proteins have distinct properties. For example, MRP1 but not MDR1 transports negatively charged natural product drugs [16]. ABCG2/BCRP interacts with heme and other porphyrins in a manner that exemplifies the tissue defense properties of the efflux pumps [15], which are capable of transporting toxicants (cationic, anionic, neutrally-charged), environmental carcinogens, metals, pesticides, and lipid peroxidation products. Of particular interest are the lipid-transporting properties displayed by some of the ABC proteins [17].

## 3. How ABC transporters impact response to drugs

Among the myriad effects of P-gp on drug disposition and interaction is the restriction of intestinal absorption; a comparative study found that plasma concentrations of HIV protease inhibitors (indinavir, nelfinavir), which have poor absorption, were 2 to 5 times greater in mdr1a (−/−) mice than in wild-type mice [18]. Absolute bioavailability of the HIV drugs was 22% in normal mice, as compared with 72% in the knockout mice. Another murine study demonstrated that limited oral bioavailability of paclitaxel was in part due to P-gp-mediated direct excretion of drug from systemic circulation into the intestinal lumen [19]. Grepafloxacin, an oral fluoroquinolone active against *S. pneumoniae* and pneumococcal pneumonia [20], is a substrate for two ABC transporters, MDR1 and MRP1 [21]. Bioavailability of fluoroquinolones is unfortunately limited by P-gp-mediated biliary excretion [22]. CPT-11, an analog of camptothecine, also exhibits extensive biliary excretion [23]. ABC transporter proteins also play a role in resistance of *Plasmodium falciparum* to antimalarials [4], and resistance of *Leishmania* to chemotherapy [5], a parasitic protozoan responsible for some of the most devastating and prevalent diseases of humans. The role of efflux in macrolide resistance (erythromycin, clarithromycin, azithromycin) is clinically significant for key pathogens such as *S. pneumoniae*, *S. pyogenes*, *Haemophilus influenzae*, and *Escherichia coli* [6]. Exaggerated drug effluxing also poses barriers to successful treatment of cancer.

Poor response to chemotherapy is usually due to drug resistance [1,7]. Approximately 40% of cancer patients with resectable disease and 80% of cancer patients with unresectable disease have poor response to chemo- and radiotherapy. In breast cancer alone, nearly 50% of patients demonstrate primary and/or secondary resistance to doxorubicin [24]. The prevalence of drug resistance in prostate and ovarian malignancies prevents significant cure with current chemotherapeutic regimens. In melanoma, which is characterized by high risk for early metastasis, the commonly employed front-line anticancer drugs do not improve prognosis [25]. In small cell lung cancer, acquired resistance to multiple drugs is responsible for a chemotherapeutic cure rate below 10% [26].

P-gp plays an important role in cancer chemotherapy [27]; it is expressed in many types of untreated malignancies, including breast, colon renal, and ovarian cancers, neuroblastoma, acute myeloid leukemia, non-Hodgkin's lymphoma, and multiple myeloma [reviewed in Drug Resistance Updates 1, 190–200, 1998, [28]. Exposure to chemotherapy can also upregulate P-gp expression, as occurs in acquired drug resistance [29,30]. In breast cancer for example, a study by Rudas et al. [31] revealed that expression of P-gp was 55% before chemotherapy and 100% after chemotherapy. Breast cancers treated by neoadjuvant therapy with fluorouracil, doxorubicin, and cyclophosphamide responded with similar enhancement [32].

## 4. Lipids in cancer

Among the richest of the vast amount of literature on lipids and cancer, are the works of Fred Snyder, Robert Wykle, and Ten-ching Lee and colleagues, specifically on ether-linked lipids in neoplasms [33–35]. Reviews appear periodically on the many aspects of lipids, the newest entries discussing prostaglandins, non-steroidal anti-inflammatory drugs and arachidonic acid metabolism in colorectal and other cancers [36,37], and the effects of omega-3 fatty acids on cancer risks [38]. Today's message suggests there is no significant association between omega-3 fatty acids and cancer incidence.

Because of the varied types of glycosphingolipids that compose cellular membranes and the trafficking and communication that occurs across these lipid (and protein) barriers, glycolipid biology and chemistry has been of particular interest in cancer research (see Fig. 1 for an abridged schematic of ceramide metabolism). Lipids, including glucosylceramide, lactosylceramide, and gangliosides, play an essential role in cell development, cell death, tumor progression, and pathogen/host interaction [39–41]. For example, radioresistant melanoma cells rich in gangliosides, can be made radiosensitive by exposure to either fumonisin B1, which blocks ganglioside biosynthesis at the juncture of ceramide synthase, or *Vibrio cholerae* neuraminidase, which cleaves cell surface gangliosides. Conversely, adding bovine brain GM1 to radiosensitive melanoma cells can confer radioresistance [42]. Studies have also shown that tumor ganglioside metabolism plays a significant role in modulating tumor formation and progression. For instance, glucosylceramide synthase (GCS) inhibition using

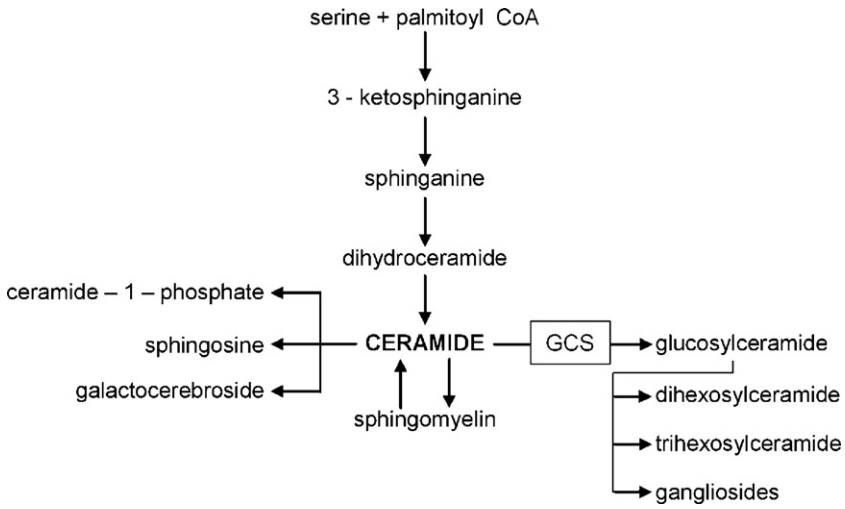


Fig. 1. Ceramide metabolism pathway.

the imino sugar, N-butyldeoxynojirimycin (NB-DNJ) in a murine melanoma model, produced a delay in tumor development [43]. Similar imino sugars that inhibit GCS, such as OGT2378, limit glycosphingolipid synthesis in melanoma cells without antiproliferative or cytotoxic effects *in vitro*, but do show marked inhibition of melanoma growth *in vivo* [44]. Studies with tumor gangliosides have demonstrated their potential as markers. In melanoma patients, serum total ganglioside levels correlate with clinical course post-therapy [45], and in organ-confined versus metastatic androgen-receptor-negative prostate cancer, ganglioside patterns may provide keys to vaccine design [46].

Glycosphingolipid composition studies in MCF-7 and MDA-MB-231 breast cancer cells showed that ganglioside content was 4-fold higher in the more aggressive, hormone-independent MDA-MB-231 cell line. In particular, GM3 levels were 18-fold higher in MDA-MB-231 cells. This may have important implications, because GM3 is thought to be involved in regulation of growth factor function [47]. In Lewis lung carcinoma cells, treatment with D-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (D-PDMP), a GCS inhibitor that limits glycosphingolipid production, reduced the lung-colonizing capacity of cells in inoculated mice by 70%. After removal of PDMP, cancer cell capacity to metastasize was completely restored [48]. Another study involving cerebrosides demonstrated that lactosylceramide supplements to human fibroblasts modified integrin function by modulating integrin clustering in microdomains and by regulating integrin endocytosis via caveolae [49]. This suggests that aberrant levels of glycosphingolipids found in cancer cells influence cell attachment events by direct effects on integrin clustering and internalization [49]. Our studies have shown that addition of glucosylceramide (short-chain analog) to the medium of cultured epidermoid carcinoma cells, enhanced *MDR1* gene expression [50].

Studies in animal models have also demonstrated a connection between glycolipids and tumor development. For example, melanoma cells depleted of endogenous gangliosides by treatment with 1-phenyl-2-hexadecanoylamino-3-pyrrolidino-3-propanol (PPPP) show poor tumorigenic capacity when injected into mice [51]. After 4 weeks, only 40% of the mice developed tumors compared with 100% of mice injected with mock-PPPP treated melanoma cells [51]. Another study in melanoma employed antisense transfection to target GCS [52]; in this genetic approach, by regulating glycosphingolipid synthesis, only 2% of mice injected with antisense-transfected melanoma cells formed tumors, compared to approximately 50% of mice in control groups [52].

## 5. Glycosphingolipids in drug-resistant cancer cells

A comprehensive review by Pallarés-Trujillo et al. [53] discusses the role of cholesterol, phospholipids, and phospholipases on drug influx and the effect of lipid composition on P-gp transport. Until the mid-1990s, relatively few works have been directed at studies of glycolipids in drug resistance. Some of the first studies demonstrated that drug-resistant cancer cell lines accumulate glucosylceramide [54,55]. For example, multidrug-resistant MCF-7-AdrR breast cancer and KB-V-1 epidermoid carcinoma cells contain higher levels of glucosylceramide than their drug-sensitive counterparts, MCF-7 and KB-3-1 [55,56]. The doxorubicin-resistant human ovarian carcinoma cell line, A2780AD, has 3-fold higher level of glucosylceramide and galactosylceramide compared to wild-type A2780 cells [57]. Also, the fenretinide-resistant A2780 cell line has been characterized by a 6-fold higher expression of ganglioside levels, notably GM3 and GM2, when compared to fenretinide-sensitive wild-type cells [58]. NIH:OVCAR-3, a human ovarian adenocarcinoma cell line established from a patient resistant to doxorubicin, melphalan, and cisplatin, also expresses high levels of glucosylceramide [55]. Moreover, analysis of tumors from selected cancer patients who failed to respond to chemotherapy treatment demonstrated elevated glucosylceramide levels [55]. These studies point to the utility of glucosylceramide as a marker of multidrug resistance.

## 6. Manipulation of glycosphingolipid levels

Studies have demonstrated that drug sensitivities can be altered by manipulating cellular glycosphingolipid metabolism. For example, transfecting wild-type MCF-7 cells with GCS confers resistance to doxorubicin [39]. The same transfection potentiated resistance to tumor necrosis factor alpha (TNFα) [59], a tumor-killing cytokine that regulates apoptosis via ceramide generation from sphingomyelin [60]. The reverse scenario has been demonstrated by transfecting MCF-7-AdrR (multidrug resistant) cells with GCS antisense, a maneuver that conferred sensitivity of the cells to anthracyclines, *Vinca* alkaloids, and taxanes [61,62]. Antisense GCS transfection can also decrease the growth rate of neuroepithelioma cells and limit tumorigenicity in melanoma [52,63]. Recently, antisense oligodeoxyribonucleotides to GCS have been used to enhance doxorubicin sensitivity in multidrug-resistant breast and ovarian cancer cells [64], and similar results have been demonstrated through use of the "P-drug" inhibitors of GCS, such as 1-phenyl-2-palmitoylamino-3-morpholino-1-propanol (PPMP). P-drugs are structural analogs of glucosylceramide, the natural GCS substrate [65]. MCF-7-AdrR cells exposed to PPMP become sensitive to anticancer agents [50]. In neuroblastoma cells, D,L-*threo*-PDMP increases sensitivity to paclitaxel and vincristine [66]. Other studies have shown that combining D,L-*threo*-PPPP, a chemical cousin of PPMP, with vincristine increases apoptosis levels in CCRF-CEM leukemia cells over vincristine alone [67]. A study by Nicholson et al. [68] also demonstrated that PPMP and PPPP preferentially kill drug-resistant variants of KB-3-1 cells. These studies suggest that limiting the synthesis of glycolipids could be one approach to dampening drug resistance. Along these lines, MCF-7-AdrR cells transfected with a GCS-specific small interfering RNA (siRNA) demonstrated reduced GCS expression and enhanced chemosensitivity [69].

Enthusiasm in the area of glycosphingolipids and chemotherapy was generated by a landmark study in leukemia wherein it was shown that daunorubicin, tumor necrosis factor-alpha, Fas, and ionizing radiation stimulated ceramide generation and elicited apoptosis [70]. Subsequent works led to the notion that targeting enzymes of ceramide clearance might allow for increases in endogenous levels of ceramide, leading to improved cytotoxic responses to chemotherapy in tumor cells. In a study by Selzner et al. [71], ceramide analogs were employed to block ceramidase in metastatic human colorectal cancer, causing cell death that was facilitated by increases in intratumoral ceramide content with activation of apoptotic cascades. Similarly, in a nude mouse model, this approach completely prevented colorectal tumor growth. A study in prostate cancer has also demonstrated the utility of inhibiting ceramidase to increase ceramide levels *in vitro* and *in vivo* [72]. Work by Lavie et al. [73] demonstrated that agents commonly employed to block P-glycoprotein such as tamoxifen, cyclosporine A, and verapamil, also retarded ceramide clearance by inhibiting ceramide glycosylation. For example, triphenylethylene antiestrogens, such as tamoxifen, blocked conversion of ceramide to glucosylceramide [73,74], thereby promoting increase in cellular ceramide. Although increases in ceramide with tamoxifen alone were moderate, combining tamoxifen with agents such as doxorubicin [75] or the cyclosporin A analog, SDZ PSC 833 (Valspodar), increased ceramide levels by as much as 11-fold, and had marked antiproliferative impact [76].

Other works have demonstrated the therapeutic benefits of manipulating glycosphingolipid metabolism. For instance, in colorectal cancer cells, when glucosylceramide production is blocked by PPMP, irinotecan-induced cell death increases by 88%, compared to irinotecan alone [77]. In neuroblastoma, PDMP treatment can increase sensitivity to paclitaxel and vincristine [66]. In another study in neuroblastoma cells, fenretinide exposure induced ceramide generation, enhanced glucosylceramide synthase activity, and promoted GD3 accumulation through increased GD3 synthase activity; these effects associated with the production of reactive oxygen species (ROS) and apoptosis [78]. The authors concluded that fenretinide-mediated apoptosis was orchestrated by sphingomyelinase, GCS, and GD3 synthase.

Although many studies demonstrate the importance of GCS in regulating chemosensitivity, work with GCS inhibitors such as the imido sugar derivative N-nonyl-deoxygalactonojirimycin, at millimolar concentrations [79], and studies conducted with specific cancer cell types, such as GM95 mouse melanoma [80], do not support the idea of targeting GCS to enhance chemotherapy response. Nevertheless, miglustat, an imido sugar that reversibly inhibits GCS, is indicated for treatment of patients with type 1 Gaucher disease, although its use is associated with significant side effects [81]. It is clear that altering GCS activity, either chemically or genetically, has been helpful in illustrating the impact of ceramide metabolism on cellular response to anticancer drugs, with some studies showing selectivity in cancer versus normal cells. For example, PDMP treatment has been shown to sensitize MCF-7-AdrR and P-gp-overexpressing MDA-MB-435 cells to paclitaxel and vincristine but not alter the chemosensitivity of the wild-type cell lines [82]. Other work on GCS and chemotherapy responses has shown that the cytotoxicity of 4-HPR, N-(4-hydroxyphenyl) retinamide or fenretinide, a potent ceramide generator [78,83], could be enhanced in ten different tumor cell lines by the addition of PPMP and other modulators of ceramide metabolism [84]. A recent study by Sun et al. [85] demonstrates that GCS knockdown by RNA interference reverses multidrug resistance in human breast cancer cells. In a study of radiation resistance, a combination of three inhibitors of sphingolipid metabolism elevated ceramide levels and reversed resistance to radiation in squamous cell carcinoma [86]. This suggests that manipulation of ceramide metabolism may offer new opportunities for overcoming radioresistance in cancer, a subject that has been recently reviewed [87].

## 7. P-glycoprotein and glycosphingolipids

P-gp can function as a broad-specificity outwardly-directed flippase for simple glycosphingolipids and membrane phospholipids [88,89]. Interestingly, overexpression of GCS and

MDR1 coincide in multidrug-resistant breast cancer, leukemia, melanoma, colon cancer, and epidermoid carcinoma (head/neck) cells [90]. This relationship was shown clearly in the head/neck carcinoma cell line KB-3-1 and its vinblastine-resistant sublines KB-V.01, KB-V.1, and KB-V1, listed in order of increasing multidrug resistance. In this model, GC, GCS mRNA, GCS protein, and P-gp increased with increased vinblastine selection pressure. Thus, selection pressure for natural product drug resistance not only upregulates MDR1 [1,29,30], but enhances ceramide metabolism through GCS. Kok et al. [91,92] have reported similar findings in HT29 colon cancer cells selected for colchicine resistance. In their study, increases in glucosylceramide levels occurred concomitantly with upregulation of MRP1 expression, showing that the two are tightly connected. Although the levels of glucosylceramide were higher, GCS expression and activity were not upregulated in the colchicine-resistant model. Our group recently showed that GCS inhibition via either GCS antisense, PPMP treatment, or GCS siRNA, downregulated the expression of MDR1 in multidrug resistant cancer cells [50]. For example, treatment of multidrug-resistant epidermoid carcinoma cells with PPMP induced an 84% decrease in MDR1 mRNA levels, with a P-gp protein level drop of 50%, compared with untreated control [50]. In a human ovarian cancer cell model, sphingomyelin, galactosylceramide, and glucosylceramide levels were significantly elevated in P-gp-overexpressing cells compared to wild-type cells [57]. In hepatoma it was shown that lactosylceramide was elevated in the MDR1-overexpressing cell line, a result of transcriptional upregulation of the enzyme, lactosylceramide synthase [93]. Other support for a link between glycolipids and multidrug resistance can be found in work showing that PPMP exposure modulates the expression of MDR1 (mRNA) in doxorubicin-resistant human ovarian cancer cells [94]. Further, in multidrug-resistant, P-gp-expressing epidermoid carcinoma cells, high GCS expression was shown to be linked to resistance [83]. A recent study in cholesterol metabolism showed that depletion of membrane cholesterol altered P-gp localization and abolished efflux [95]. These works suggest that lipids play an important role in the expression and function of the multidrug resistant phenotype [50]. Another study, however, demonstrates that decreasing the levels of ceramide in leukemia cells, by activation of GCS and sphingomyelin synthase, promoted chemoresistance through Bcl-2 and not MDR1 expression [96].

Several studies have entertained the notion that the P-drugs interact with P-gp, similar to pump antagonists such as verapamil or cyclosporine A. In hepatoma cells, PDMP has been shown to moderately inhibit P-gp activity and potentiate apoptosis that is induced by doxorubicin exposure [97]. In neuroblastoma, PDMP treatment decreases efflux of paclitaxel and vincristine, similar to the P-gp antagonist, SDZ PSC 833, suggesting an effect of PDMP on P-gp function [66]. A study in drug-resistant leukemia cells showed P-gp function was stimulated by gangliosides, whereas glucosylceramide, lactosylceramide, and ceramide had no effect [98]. In that study, gangliosides were thought to be important P-gp regulators, perhaps through their capacity to modulate P-gp phosphorylation. In studies of sphingolipid composition in human neuroblastoma, cells with high MDR1 and MRP1 expression and functional activity contained higher sphingolipid levels compared to neuroblastoma cell lines with poor ABC transporter activity [99]. Another study showed that P-gp-positive cell lines (KG1a, TF-1) were resistant to apoptosis induced by C8-ceramide, compared to P-gp-negative cell lines (HL-60, U937) [100]. The same study showed that glucosylceramide inhibited P-gp activity in TF-1 cells, and that P-gp inhibition by cyclosporin A and GF120918 decreased GCS activity, lactosylceramide formation, and rhodamine 123 accumulation in the Golgi of TF-1 cells. These results indicate that the influence of P-gp on glucosylceramide metabolism contributes to the resistance of P-gp-positive TF-1 cells to ceramide-induced apoptosis [100].

## 8. Conclusions—lipids and the MDR1 phenotype

Glycosphingolipids impact cellular sensitivity to anticancer agents, in particular the natural product, ceramide-generating chemotherapy drugs. It is also well accepted that ceramide drives cell death signaling elicited in response to exposure to

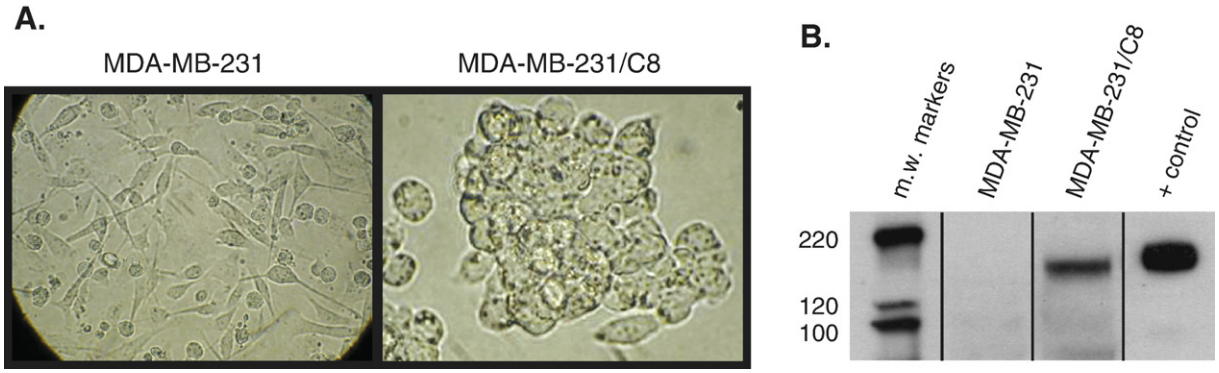


Fig. 2. Influence of C8-ceramide exposure on morphology and P-glycoprotein expression in MDA-MB-231 human breast cancer cells. Cells were grown for 12 passages in culture medium (RPMI-1640, 10% FBS) containing C8-ceramide (5.0 μg/ml). (A) Photomicrograph of wild-type MDA-MB-231 (400×) and C8-ceramide supplemented MDA-MB-231/C8 (400×). (B) Western blot using C219 monoclonal antibody to P-gp. 100 μg total cell protein was loaded for MDA-MB-231 and MDA-MB-231/C8 cells. MCF-7-AdrR (doxorubicin-resistant MCF-7 cells) were used as + control (positive control), and 0.25 μg total cell protein was loaded. m.w. denotes molecular weight markers.

chemotherapeutics. Cell-permeable ceramide analogs have even been shown to stimulate monocytic differentiation in human promyelocytic leukemia [101]. The notion, however, of ceramide and glycolipids imparting drug resistance has not been explored. In an attempt to answer this question, we exposed wild-type, P-gp-negative MDA-MB-231 breast cancer cells to low dose C8-ceramide for extended passages. Cells (passage 12) were then evaluated and compared to the ceramide-naïve MDA-MB-231 counterpart. Fig. 2A (photomicrograph) shows that the C8-ceramide-grown cells (MDA-MB-231/C8) were rounder, larger, and tended to grow in islands consisting of clumped, multilayered cells, compared to wild-type MDA-MB-231 cells. In addition, MDA-MB-231/C8 cells had significantly higher levels of MDR1 mRNA (45-fold) compared to MDA-MB-231 cells. Fig. 2B shows P-gp expression as determined by Western blot. Compared to MDA-MB-231 cells in which P-gp was undetectable under these conditions, MDA-MB-231/C8 cells expressed relatively high levels of P-gp. These findings indicate that lipids elicit expression of the multidrug-resistant phenotype in human cancer cells. Ceramide's role as a messenger of cytotoxic response to chemotherapy may be linked to the multidrug resistance pathway.

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